Facility Report:

Jigme Dorji Wangchuck National Referral Hospital, Bhutan

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CAPTURA
Capturing data on Antimicrobial resistance Patterns and Trends in Use in Regions of Asia

MOTT MACDONALD

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Part I: General Introduction

Aim

This report has been prepared by the CAPTURA team to share apparent findings and observations from the project metadata and AMR/U data shared by your facility. It also provides feedback and recommendations on data management and quality based on the experiences of the in-country team.

Introduction

Capturing data on Antimicrobial Resistance Patterns and Trends in Use in Regions of Asia (CAPTURA) fosters a two-fold aim:

- To increase the volume of available data on antimicrobial resistance (AMR), antimicrobial use (AMU), and antimicrobial consumption (AMC)
- To illustrate data availability and capacity of laboratories generating those data

Local governments and facilities in 10 South or Southeast Asian countries were engaged. Among these, AMR, AMU, and/or AMC data were collected from 8 countries, including Bangladesh, Bhutan, Laos, Nepal, Pakistan, Papua New Guinea, Sri Lanka, and Timor-Leste. The collated data are analysed to paint a local overview and to understand data availability in regional and inter-regional contexts wherever possible. CAPTURA's findings may inform future initiatives in bolstering awareness, policy, and interventions to combat the urgent global threats of spreading AMR and antimicrobial misuse.

CAPTURA is funded by the Fleming Fund Regional Grant.

Description of data activities

To meet CAPTURA's two-fold aim, two distinct types of data were collected: namely, source data and project metadata. The source data includes AMR, AMU, and AMC data, which were collected/generated by local facilities (microbiology laboratories, pharmacies, or central government procurement and distribution agencies). The project metadata constitutes all information collected directly by the CAPTURA consortium, via questionnaires developed specifically for the purpose of CAPTURA. These include Laboratory/Pharmacy Questionnaires and Rapid Laboratory Quality Assessment (RLQA).

To optimize the data collection process, extensive mapping activities took place by engaging local governments and data-holding facilities. Laboratory capacities as well as the quality of data from each facility were assessed, which were also used to identify areas for quality improvement at an individual-facility level. Data collection primarily focused on a four-year timeframe between 1 January 2016 and 31 December 2019, but also included data from 2020 and 2021 for certain sites.

Throughout the project, capacity-building activities have taken place to help facilities collate and curate data in a standardized format. These capacity-building activities also extend the aims of CAPTURA to help improve local data management practices.

Engagement with JDWNRH

Jigme Dorji Wangchuck National Referral Hospital (JDWNRH) was introduced to the CAPTURA consortium during the initial scoping visit via the liaison of the Bhutan Ministry of Health. Through signing the Data Transfer Agreement (DTA), the laboratory agreed to isolate level AMR data sharing and to allowing the data to be shared with Health Care and Diagnostic Division, Department of Medical Services, Ministry of Health. CAPTURA formed an in-country team who mediated communications with sites, engaged local stakeholders, and collected data during the project period.

Part II: AMR Data Analysis

The microbiology laboratory at JDWNRH shared its isolate level susceptibility data for the time frame of January 2017 to December 2019. The CAPTURA in-country team led the efforts to digitize the AMR records from the and entering the data into the WHONET software. CAPTURA's in-country microbiologist conducted a thorough review to identify typos and errors in the data, after which Dr. John Stelling and the WHONET team conducted a review to understand the quality of data. Before sharing data with CAPTURA, patient identifiers were removed (e.g., patient name) and encrypted (e.g., patient ID). The data files were then uploaded to the CAPTURA Warehouse. The facility also participated in project's metadata activities, including the Rapid Laboratory Quality Assessment and Laboratory Questionnaire.

Data Analysis disclaimer
The dataset can be analysed using the 'Data Analysis' and 'Quick Analysis' features in the WHONET software. The Quick Analysis feature allows both the Epidemiological and Data Quality reports to be exported in a word document. The interpretation and graphical representation in this report is, however, a combined outcome of the WHONET software and CAPTURA AMR Data Visualization Tool. Additional curation (e.g., combining sub-species, reassigning categories to ensure alignment with WHONET software) and interpretation were conducted by the CAPTURA Data Team to provide the facility a detailed report. Therefore, the reports will not be identical to those generated from WHONET software alone.

Epidemiology Report

1 Data Volume

JDWNRH has shared bacteriological culture records, with a total of 89,871 observations over the period of January 2017 to November 2019 (Figure 1). Of these observations, 34,293 had bacterial growth reported as positive cultures. The shared dataset includes all variables considered essential to a complete AMR dataset, except for the patient location variable.

Table 1. List of expected variables included or missing in the shared dataset. Expected variables are variables that CAPTURA considered essential to a complete AMR dataset.

Expected Variables included in the dataset	Expected Variables NOT included in the dataset
Patient Identification number	Patient Location (Ward/Clinic)
Age	
Sex	
Specimen Number	
Specimen Type	
Specimen date	
Organism	
Department	

Table 2. The number of culture records over time. For each year, the number indicates the number of culture records, including bacterial growth and no growth results.

Data volume overview								
	Cumulative	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**NULL**
Number of records	89871	0	34580	38193	17098	0	0	0
Bacterial Growth	34293	0	12607	14623	7063	0	0	0
No Growth	55578	0	21973	23570	10035	0	0	0

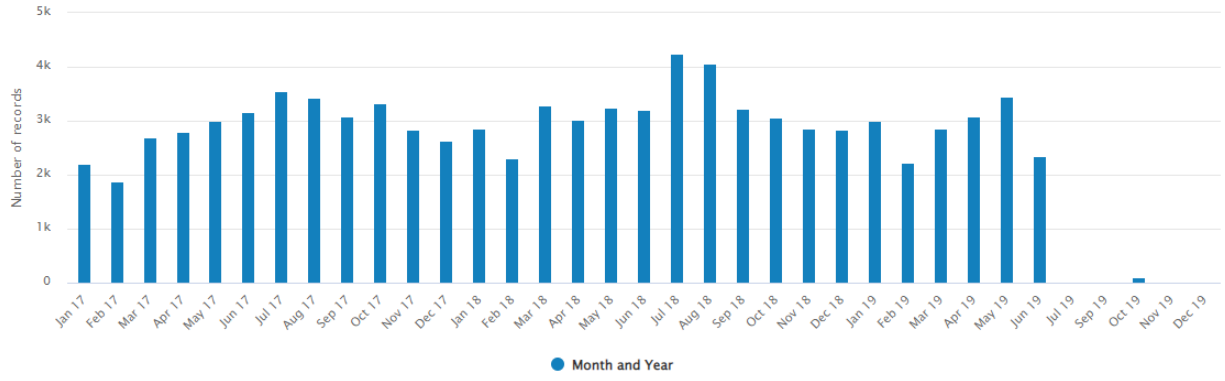

Figure 1. The distribution of the number of culture records over time, including negative results.

Documenting the volume of testing performed by a laboratory is useful for monitoring changes in sampling practices over time and for comparing the workloads between laboratories. One may also identify time periods where data entry is incomplete; for instance, many laboratories experienced a significant decrease in bacteriological testing in April-May 2020 with the arrival of COVID-19.

2 Patient Demographics and Sample Details

2.1 Sex and Age

The AMR dataset from JDWNRH has the distribution of patients by sex and age group as follows:

- **Sex**: Female: 60.5% (N = 53861), Male: 39.5% (N = 35167)
- **Median age group**: Female = 25-34 years old, Male = 25-34 years old

In many countries, the number of samples from female patients exceeds the number of samples from male patients for the following reasons:

1) A large proportion of laboratory samples are often from urinary tract infections in women.

2) Women may seek medical assistance more frequently than men.

3) In many countries, women have a longer lifespan than men. The age distribution will reflect the patient population served by the laboratory.

The observation of a slightly higher number of females than males in the shared dataset is a normal finding as detailed above. Records of a higher number of females of reproductive age (25-34 years) is also expected, as females in this group are more prone to urinary tract infections (Figure 2). Laboratories typically receive mostly urine samples for culture from this group.

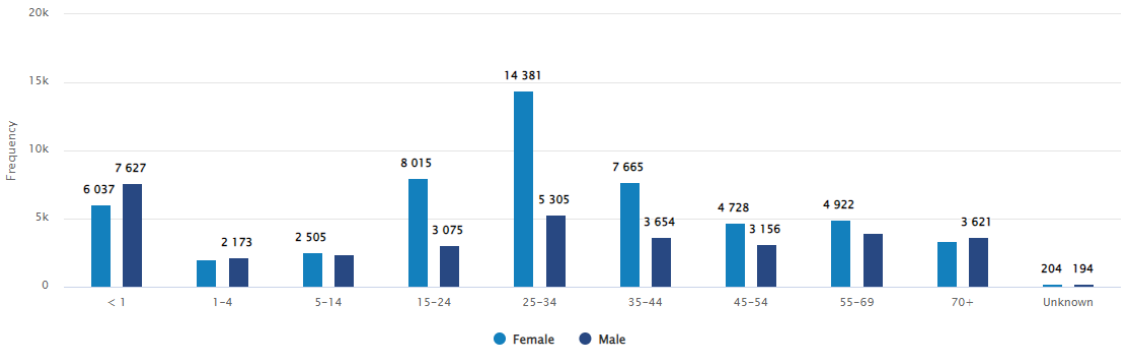

Figure 2. Distribution of the number of patients by sex and age group for all records.

2.2 Location

The location variable generally refers to the specific location where samples originated from. For the JDWNRH microbiology laboratory, this would include the ward or department information, such as "Neurology", or "Diabetes clinic".

Location type is a category of location such as "inpatient" or "outpatient". It will be beneficial to use standard WHONET codes to standardize the dataset across laboratories and facilitate the comparison of results between laboratories, but this is not an absolute necessity.

Keeping information on the origin of the samples will help a facility to understand the types and volume of samples being processed at each location and help facilities plan logistics required at the department. Moreover, it allows the facilities to understand the resistance patterns of the pathogens being isolated in the clinics and allows the clinicians/researchers/public health experts to identify local outbreaks within the facility and take appropriate actions.

Table 3. The distribution of samples and patients by location. The location codes are those used by the laboratory to identify the specimen collection site. The abbreviations indicated here are location codes provided by the laboratory. It is recommended to accompany abbreviations with a data dictionary for interpretation.

Location	Number of samples	(%)	Number of patients	Samples per patient
opd	41,429	46.1	38,112	1.1
cty	10,652	11.9	10,217	1
rba	5,872	6.5	5,752	1
nicu	5,288	5.9	4,631	1.1
mew	3,734	4.2	3,274	1.1
pew	3,618	4	3,533	1
suw	2,887	3.2	2,712	1.1
cab	2,301	2.6	2,018	1.1
orw	2,006	2.2	1,919	1
derw	1,995	2.2	1,716	1.2

Q. Why care about "Isolates per patient"?

A. This metric quantifies the average number of records available from patients over time. In low-resource settings, this number is typically low, between 1.1 and 1.5 records per patient. A low number of samples per patient may indicate that there are few patients for which multiple samples were collected. It is recommended to provide a unique patient identification number to confirm this observation. If a dataset is missing a link between a patient and samples collected from that patient, it suggests that there are no meaningful patient identification numbers that can be used to track patients over time. A higher number may suggest issues, such as 1) patient identification numbers are reused for different patients over time; and 2) there may be a problem in the data export from a laboratory information system or in the BacLink configuration. CLSI recommends analysing the first isolate per species in the time period.

2.3 Sample Details

WHONET categorises specimen types into eight broad categories: Blood, Genital, Respiratory, Soft tissue and body fluids, Stool, Urine, Other, and Unknown. In the secondary curation conducted by the CAPTURA team, the Other and the Unknown categories were combined under Other.

Urine was the most common specimen subjected to the bacterial culture at JDWNRH, followed by blood, then soft tissue and bodily fluids specimens. When a subset of samples that showed growth was further analysed, the order changed to urine, then soft tissue and bodily fluids, and then blood specimens (Figure 3).

It is a normal observation in laboratories with microbiological culture facilities to have a relatively large number of urine samples, as it is the most frequently processed sample for culture. Additionally, it is a regular observation that the samples were obtained from females as the number of female patients tends to be higher.

Culture positivity rate of blood culture is usually low (range 3-25%) in most regular clinical laboratories as the isolation rate depends on various factors including the clinical condition, ambulatory or hospitalized state, length of hospital stay, age of the patient, and several other factors. Thus, the change in the order when only samples with bacterial growth were analysed is a normal finding. In the context of JDWNRH, the blood culture positivity rate is 14.3%, which is within the normal range.

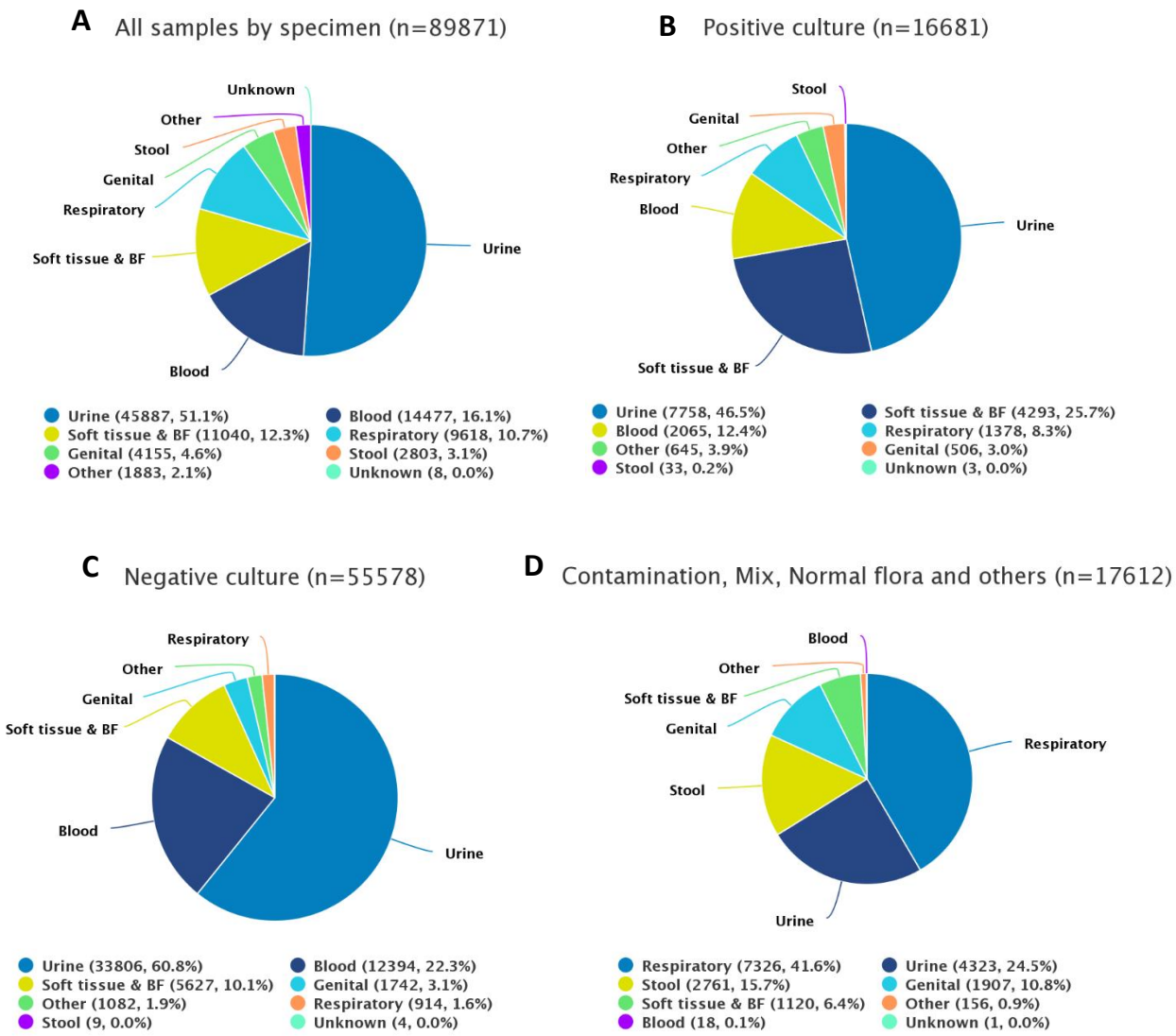

Figure 3. The number of culture records stratified by specimen category. Cumulative records including both culture positive and negative finding (**A**). Showing only those with growth true pathogens (**B**). Showing only culture negative results (**C**). Showing growth with contamination/normal flora/mixed flora and others (D).

3 Organism Statistics

3.1 Organism Frequencies

Looking into the most frequently isolated organisms in all samples, *Escherichia coli,* coagulase-negative *Staphylococcus, Klebsiella* sp., *Staphylococcus aureus ss aureus,* and *Streptococcus* sp. were the top five most isolated organisms found in the JDWNRH dataset (Figure 4).

This correlates well with the fact that most common sample in the dataset was urine, as *Escherichia coli* is often the most frequently reported pathogen in urine cultures (Figure 5). In the JDWNRH shared dataset, coagulase-negative *Staphylococci* was the second most frequent organism isolated from all samples. Further analysis of the frequency of organisms from each sample showed that coagulase-negative *Staphylococci* was the most frequent organism isolated from soft tissue and bodily fluids and blood samples. This needs to be verified and correlated clinically, as coagulase-negative *Staphylococci* are usually found as skin flora and are considered contaminants unless repeatedly isolated from paired samples or in subsequent samples collected over a period. Also, it is unusual that coagulase-negative *Staphylococci* was isolated more frequently than *Staphylococcus aureus*, as the latter is both more pathogenic and associated with causing more infections than the former. Laboratories must rule out between contaminants or pathogens associated with bacteraemia or infection of other sites (e.g., where there is possible contamination with skin flora while collecting samples) to prevent additional lab tests, unnecessary antibiotic use, and longer hospital length-of-stay for patients, all of which increase the cost of patient care. It is also worth noting that pathogens *Klebsiella* spp. and *Staphylococcus aureus* were other frequently isolated organisms in this setting. As the time of patient admission or onset of the disease were not recorded, it is not possible to comment if these pathogens were from hospital-acquired infections or community settings. However, these organisms are potential nosocomial pathogens that are mostly MDR and are associated with high mortality and morbidity in hospitalized patients. It is worth noting that JDWNRH is a national referral hospital that caters to referred cases from all over the country and provides health care to severely ill patients requiring extended hospital stays and/or prolonged antibiotic use. It is thus essential that the hospital strictly follows infection control practices to prevent the spread of these organisms in hospital as well as community settings.

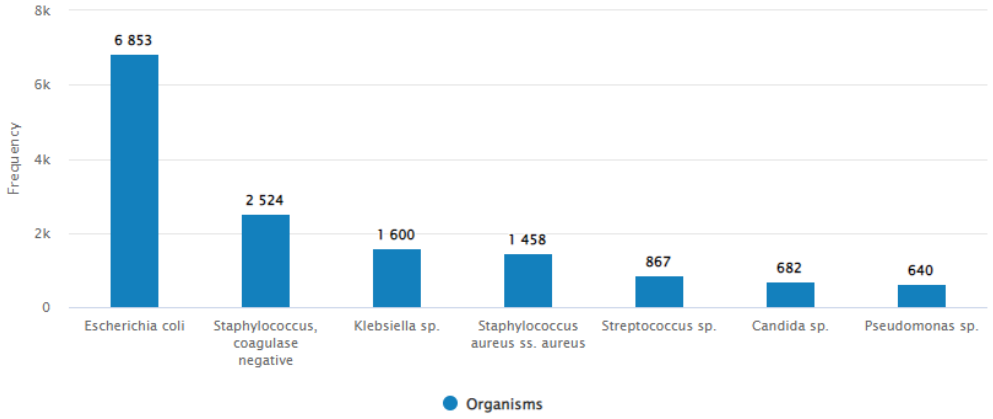

Figure 4. Most common organisms isolated from all samples over the reported period.

WHONET has categorised some pathogens as "important species". Such pathogens are considered important for public health because of their potential for outbreaks and thus often included in national disease control programs.

Table 4. Public health alerts - important species.

Organisms	Number of isolates	Priority	JD	JD2	BAC
Neisseria gonorrhoeae	4	High priority	2	2	
Neisseria meningitidis	2	High priority	1	1	
Salmonella Typhi	12	High priority	9	3	
Salmonella sp.	97	Medium priority	74	12	11
Pseudomonas aeruginosa	506	Medium priority	248	158	100
Streptococcus sp.	18	Medium priority	10	6	2

Twelve isolates of *Salmonella* Typhi were also identified as high priority pathogens categorised by WHONET. This finding is consistent with the fact that typhoid is endemic in Bhutan, and a large number of cases are reported every year with frequent outbreaks. Although 97 isolates of *Salmonella* spp. were not identified up to the species level and were categorised as medium priority pathogens, they are likely typhoid bacilli (*Salmonella* Typhi/Paratyphi) as they were isolated from blood and stool samples; they should thus be considered high priority pathogens. The identification of other high priority pathogens, *Neisseria gonorrhoeae* and *Neisseria meningitidis,* is significant as infections caused by these pathogens remain an important public health concern in Bhutan. Identification of high priority pathogens in the facility will contribute to early diagnosis and treatment and help prevent the spread of the bacteria. If possible, it is recommended to preserve these high priority isolate/s for future studies.

A large number of samples also yielded medium priority pathogen *Pseudomonas aeruginosa,* which shows a high level of MDR and is responsible for hospital-associated infections. Eighteen isolates of medium priority pathogen *Streptococcus* spp. were also reported. Although not identified up to species level, the genus *Streptococcus* has some important species that are pathogenic; if some species acquire resistance, they can cause outbreaks in hospitals. Therefore, it is necessary to monitor frequency and pattern of isolation of these medium priority pathogens and any associated outbreaks.

Figure 5. Most common organisms by specimen category. Urine, Blood, Soft tissue, Respiratory, Genital and Stool.

Q. Why is it important to understand organism frequencies?

A. Understanding temporal changes in pathogen diversity in a given geographic area will help develop local/regional policies and guidelines for case management. It will also help public health experts to monitor the disease occurrence/spread and changes in the resistance pattern in the pathogen of concern. The frequency of organisms seen in a microbiology laboratory may change over time for different reasons:

- Microbial factors
    - Long-term changes in organism epidemiology related to organism dissemination, virulence factors, and disease prevention measures such as vaccination and improved sanitation.
    - Short-term changes suggestive of disease outbreaks. Statistical algorithms for automated outbreak detection are described in a separate section.

- Non-microbial factors
    - Healthcare services provided and patient populations.
    - Sampling practices.
    - Laboratory capacity and practices for organism identification.

Long-term changes in organism frequency with simple linear regression of organism counts over time is shown in Tables 5 and 6. The column "slope" in the table indicates increase (if positive value) or decrease (if negative value) in the isolation frequency.

Table 5. Organisms with statistically significant increases in organism frequency over time using simple linear regression, $p<0.05$. The slope indicates the estimated change in the number of isolates by quarter.

Organism	Q1-17	Q2-17	Q3-17	Q4-17	Q1-18	Q2-18	Q3-18	Q4-18	Q1-19	Q2-19	Slope
Trichomonas vaginalis				2		7	4	3	6	18	1.4
Vaginal flora	50	54	49	23	61	209	351	264	332	482	48.7

Table 6. Organisms with statistically significant decreases in organism frequency over time using simple linear regression, $p<0.05$. The slope indicates the estimated change in the number of isolates by quarter.

Organism	Q1-17	Q2-17	Q3-17	Q4-17	Q1-18	Q2-18	Q3-18	Q4-18	Q1-19	Q2-19	Slope
Moraxella sp.	7	8	4	3	5	6	2	4	2	4	-0.4
Streptococcus pneumoniae	22	21	18	20	24	18	16	19	12	17	-0.7

4 Antimicrobial Statistics

4.1 Antimicrobial Resistance Patterns and Trends

CAPTURA analysis includes presentation of the cumulative resistance pattern of key organisms over three years, as well as the resistance trends over the same period for key organisms for a set of antimicrobials. In the context of JDWNRH, no patterns and trends analyses are presented due to the low availability of information in the shared datasets.

Understanding antimicrobial patterns helps clinicians in routine case management, whereas monitoring antimicrobial trends is important from public health perspectives.

4.2 Gram-positive and Gram-negative Antibiograms

The appendix contains the cumulative antimicrobial susceptibility test statistics for Gram-positive and Gram-negative bacteria, typically known as an "antibiogram". The number of isolates tested is greater than or equal to 20. The official recommendation from the CLSI M39 document and others is at least 30 isolates, but a limit of 20 is still useful, especially in a low-resource setting with smaller data volumes and for organisms of clinical importance.

Policymakers must be aware of problems in laboratory test quality and different types of bias due to patient presentation, sampling practices, and laboratory test practices. Routine microbiology laboratory data typically underestimates the incidence of microbial disease but overestimates the proportion of resistance.

4.3 Isolate alerts - Important Resistance

WHONET has built-in public health alerts that signal when high- and medium priority "important resistance" has been recorded. These public health alerts are identified by WHONET. We recommend that the laboratory confirm these test results to ensure that there is no error in the organism identification or antimicrobial susceptibility test. A separate section in this report lists out the “Global Priority List of Antimicrobial Resistant Bacteria" defined by the WHO.

Table 7. The distribution of public health high priority and medium priority important resistance from JDWNRH identified by WHONET.

Organisms	Alert	Number of isolates	Priority	JD	JD2	BAC
Enterobacteriaceae	carbapenems = non-susceptible	392	High priority	176	145	71
Neisseria meningitidis	cephalosporin III = non-susceptible	1	High priority	1		
Salmonella sp.	cephalosporin III = non-susceptible	3	High priority	2	1	
Salmonella sp.	fluoroquinolones = non-susceptible	16	High priority		8	8
Salmonella sp.	nalidixic acid = non-susceptible	12	High priority	2	4	6
Streptococcus pneumoniae	fluoroquinolones = resistant	1	High priority	1		
Streptococcus, beta-haemolytic	penicillins = non-susceptible	1	High priority	1		
Enterobacteriaceae	amikacin = non-susceptible	175	Medium priority	79	70	26
Enterobacteriaceae	possible ESBL-producing *Enterobacteriaceae*	3,675	Medium priority	1,743	1,240	692
Enterococcus sp.	vancomycin-resistant *Enterococcus*	2	Medium priority	1		1
Staphylococcus aureus	methicillin-resistant *Staphylococcus aureus*	231	Medium priority	113	84	34
Streptococcus pneumoniae	penicillin-non-susceptible *Streptococcus pneumoniae*: penicillins or cephalosporin III = non-susceptible	7	Medium priority	5	1	1
Streptococcus viridans	penicillin or ampicillin = non-susceptible	10	Medium priority	2	6	2

4.4 Multidrug Resistance: (following ECDC definitions of MDR/XDR/PDR)

In a 2012 publication, the European Centre for Disease Prevention and Control (ECDC) proposed definitions for common bacterial pathogens resistant to multiple antimicrobials. MDR refers to multidrug resistance, XDR to extensive drug resistance, and PDR to pan-drug resistance. It is, however, important to note that WHONET/CAPTURA does not confirm the pathogens as truly XDR and PDR due to the limited number of antimicrobials tested. Thus, we report possible XDR/PDR on the assumption derived from the groups of antimicrobials tested and analysed by the application. Further, defining MDR, XDR, and PDR according to the local context of available antibiotics is more important than following the ECDC definitions. It is recommended that labs maintain a repository of the isolates that shows a PDR profile, and to periodically verify it with reference laboratories by sharing their results and isolates.

The JDWNRH dataset showed a high frequency of drug resistant organisms, with the most frequent organism *Escherichia coli* being nearly 30% MDR and possible PDR. The highest rate of MDR (61%) and possible XDR (59%) was exhibited by *Acinetobacter* spp., and possible PDR (8%) by *Klebsiella pneumoniae*. If correct, this is alarming and a matter of concern for the facility. We recommend using the WHONET program to periodically monitor this finding. Similarly, it is also recommended to ensure proper infection control practices and antimicrobial stewardship to prevent the emergence and spread of these strains.

Table 8. Summary of MDR, possible XDR, and possible PDR results.

Organism	Number of isolates	MDR	Possible XDR	Possible PDR
Enterococcus faecalis	3			
Staphylococcus aureus	1,458	237 (16%)	193 (13%)	9 (1%)
Acinetobacter sp.	525	322 (61%)	309 (59%)	8 (2%)
Escherichia coli	6,853	1,899 (28%)	1,899 (28%)	267 (4%)
Klebsiella pneumoniae	1,417	507 (36%)	506 (36%)	109 (8%)
Pseudomonas aeruginosa	506	49 (10%)	49 (10%)	24 (5%)

Q. Why we need antibiotic resistance profiles?

Antibiotic resistance profiles can be used for cluster analysis and other several applications:

- Phenotypic strain tracking facilitates the monitoring of distinct microbial subpopulations, greatly improving the recognition of 1) new strains, and 2) hospital and community outbreaks. Clusters identified by phenotypic tracking could be investigated by molecular typing to confirm clonality.
- The study of cross-resistance is useful in the development of treatment guidelines, including 1) the determination of recommended "first-line" and "second-line" treatment options, and 2) estimating the value of combination therapy on local pathogens.
- Predicting resistance mechanisms based on the results from antimicrobials within a specific antimicrobial class or subclass or related classes.
- Exploring potential errors in laboratory test practices. For example, the finding of isolates of *Escherichia coli* susceptible to ampicillin but resistant to imipenem is unlikely as imipenem belongs to a higher class of beta-lactam antibiotics and has a greater potency and antibacterial activity than ampicillin. This may be due to a testing error, such as using imipenem disks that have lost their disk potency.

4.5 WHO Global Priority List of Antibiotic-Resistant Bacteria

WHO defines the following list of organisms in its Global Priority List of Antibiotic-Resistant Bacteria. Priority pathogens are critical, as WHO identifies that these pathogens organisms are rapidly developing resistance to existing antibiotics and thus urgently require newer antibiotics. If any such findings are observed, labs should conduct confirmation testing to ensure that there is no error in the organism identification or in the antimicrobial susceptibility test. It is, however, important for each country to come up with its own priority list that fits the unique epidemiologic context.

Here, it is again important for the facility to confirm these results by testing again, and to keep a biorepository of these isolates. These isolates should be sent to a reference lab to confirm the findings.

Table 9. WHO Global priority list of antibiotic-resistant bacteria.

Priority	Organism	Antibiotic results	Number (%)
Critical	*Acinetobacter* spp.	carbapenem-resistant	70/417 (17%)
	Pseudomonas aeruginosa	carbapenem-resistant	31/59 (53%)
	Escherichia coli	cefotaxime-resistant	-
	Escherichia coli	ceftriaxone-resistant	2,527/6,455 (39%)
	Escherichia coli	meropenem-resistant	105/215 (49%)
High	*Enterococcus faecium*	vancomycin-resistant	-
	Staphylococcus aureus	methicillin-resistant (MRSA)	225/1,417 (16%)
	Staphylococcus aureus	vancomycin-resistant	0/10 (0%)
	Staphylococcus aureus	vancomycin-intermediate	0/10 (0%)
	Helicobacter pylori	clarithromycin-resistant	-
	Campylobacter spp.	fluoroquinolone-resistant	-
	Salmonella spp.	fluoroquinolone-resistant (ciprofloxacin)	10/96 (10%)
	Neisseria gonorrhoeae	third generation cephalosporin-resistant	0/4 (0%)
	Neisseria gonorrhoeae	fluoroquinolone-resistant	1/3 (33%)
Medium	*Streptococcus pneumoniae*	penicillin non-susceptible	0/134 (0%)
	Haemophilus influenzae	ampicillin-resistant	20/188 (11%)
	Shigella spp.	fluoroquinolone-resistant	4/5 (80%)

Key Highlights from AMR Epidemiology Report

- JDWNRH collects a basic set of variables necessary for the culture report, but patient related information is missing. Culture report and patient information variables, if collected and maintained, will allow for multiple analyses that will be helpful for the development of institutional and national guidelines and policies.
- The isolation of priority pathogens of public health importance that are MDR/possible XDR and PDR is alarming. This needs to be verified and closely monitored to prevent their spread.
- Facilities should introduce tests for screening important resistance (ESBL, MRSA, VISA/VRSA, VRE etc.) which will support RIS interpretations and supplement AST reports.
- A high level of resistance in common organisms, along with frequent isolation of pathogens associated with HAI, is a matter of concern.
- The facility should ensure testing of recommended antibiotics consistently according to standard guidelines.

Quality Report

The WHONET Quality report addresses the issue of data quality from several perspectives. The analyses include several indicator metrics that can be used to identify priority areas for improvement, to monitor improvement over time, and to compare results from different laboratories.

- **Data entry and data management:** Completeness and accuracy of data entry, antibiotic configuration, use of recommended WHONET codes
- **Laboratory results:** Organism identification, antimicrobial susceptibility test practices, quality control results

5 Data Entry and Management

5.1 Data Volume

From a data quality perspective, some of the main considerations include the below:

- **Are there any results from outside of the expected date ranges?** This may suggest an error in data entry.
- **Are there any time periods where the number of records is lower or higher than expected?** This may suggest incomplete data entry or double data entry. Data entry practices may change over time. For example, some laboratories only enter positive results when they begin to use WHONET, but over time they may expand to include both positive and negative results.

5.2 Completeness and Validity of Data Entry

Some high priority data fields include Age, Organism, Identification number, Sex, Specimen type, Specimen data, Location, and Location type. The JDWNRH dataset showed high completed % for all variables except for the identification number.

Table 10. Data entry completeness and quality metrics.

Data Field	% Completed
Age	99%
Organism	100%
Identification number	49%
Sex	99%
Specimen type	99.99%
Specimen date	100%
Location	100%
Location type	0%

6 Quality Control Testing

The regular testing of standard quality control strains such as ATCC 25922 *Escherichia coli* and ATCC 25923 *Staphylococcus aureus* is highly recommended to ensure the reliability of test results. The user can enter the results of these standard strains into WHONET.

No quality control results were found in the JDWNRH dataset shared with CAPTURA, and the practice of testing quality control was not further verified by the project. In general, it is recommended that the hospital introduce and practice internal quality control program and maintain records of such IQC activity to validate the results.

7 Organism Results

This section provides information on the capacity of lab to speciate an isolated organism. This provides valuable insights into a laboratory's capacity for isolating and identifying organisms. Broadly, this section, generated from WHONET, describes how the lab identifies organisms using general terms such as "Gram negative enteric organism," or whether the laboratory can identify organisms to the genus, species, subspecies, or serotype level such as "*Klebsiella* sp." or "*Klebsiella pneumoniae*". It also assesses whether the laboratory isolates fastidious organisms such as *Haemophilus influenzae*, *Campylobacter* sp., or anaerobic organisms.

7.1 Capacity for Organism Identification

There are many important microbes that are usually identified to the species level, for example, *Escherichia coli* and *Staphylococcus aureus*. For other microbes, it depends on the resources, capacity, expertise, and practices of the laboratory, especially for laboratories using manual identification methods.

Table 11. Level of organism identification for aerobic bacteria. *Staphylococcus aureus* and *Escherichia coli* have been excluded as most laboratories routinely identify these organisms to the species level. JDWNRH has demonstrated its high capacity for bacterial isolation and identification for most pathogens up to species level, except for *Enterococcus* sp.

Organism	% Speciated
Enterococcus sp.	/ 322 (0%)
Klebsiella sp.	1,596 / 1,600 (100%)
Pseudomonas sp.	506 / 640 (79%)
Overall	2,102 / 2,562 (82%)

7.2 Capacity for Isolation and Identification of Fastidious Organisms

Some bacteria are difficult for laboratories to isolate or identify for several reasons:

- Organisms may not be viable when the specimen arrives in the laboratory
- Special medium required for the organism to grow
- Special incubation conditions
- Special reagents required for organism identification
- Advanced knowledge and experience required by laboratory staff

Examples include *Haemophilus* sp*., Campylobacter* sp*., Helicobacter* sp*., Streptococcus pneumoniae, Neisseria* sp., *Mycobacteria* sp*.,* and anaerobic organisms.

The JDWNRH laboratory shows good capacity for the isolation of different fastidious organisms from clinical samples. Important pathogens such as *Haemophilus influenzae* and *Streptococcus pneumoniae* were isolated in large number over the reported period. However, a diagnostic laboratory should consider the clinical relevance of reporting unusual organisms and their associated impact on patient management.

Table 12. Results for fastidious organisms.

Organism	Number of isolates	(%)	Number of patients	Isolates per patient
Anaerobic Gram-negative organisms	1	0.2	1	1
Bacteroides sp.	1	0.2	1	1
Moraxella (Branh.) *catarrhalis*	3	0.7	3	1
Haemophilus influenzae	204	44.9	203	1
Haemophilus parainfluenzae	2	0.4	2	1
Moraxella sp.	46	10.1	45	1
Neisseria gonorrhoeae	4	0.9	4	1
Neisseria meningitidis	2	0.4	2	1
Nocardia sp.	1	0.2	1	1
Nocardia otitidiscaviarum	1	0.2	1	1
Rickettsia conorii	1	0.2	1	1
Streptococcus pneumoniae	188	41.4	188	1

8 Antimicrobial Susceptibility Test Practices

Clinicians and public health authorities depend on microbiology laboratories to provide reliable antimicrobial susceptibility test results. To this end, laboratories must decide which antimicrobials to test for different organism groups and by which test method. For disk diffusion tests, the laboratory must also select an appropriate disk potency. These decisions should be based primarily in recommendations from CLSI or EUCAST guidelines.

It is important to explore two aspects of antimicrobial susceptibility test practices:

- **Appropriateness of antimicrobial selected**: Many laboratories test antimicrobials that have no validated CLSI or EUCAST breakpoints. For example, there are no breakpoints for cephradine and there are no breakpoints for imipenem and *Staphylococcus aureus*.
  Regularity of testing: Laboratories often test antimicrobials inconsistently, for reasons such as stock outages of required disks or changes in purchases over time. There is often insufficient appreciation of the importance of consistent testing for clinical reporting and antimicrobial resistance surveillance.

8.1 Antibiotic Configuration

Antimicrobials with no results in the data files analysed are also indicated. If there were no plans to enter and analyse results from these antimicrobials, they were removed from the laboratory configuration.

Table 13. Antibiotics defined by the laboratory, configured on the WHONET specifically for JDWNRH Laboratory.

Guidelines	Test method	Number of antibiotics	Antibiotics
CLSI	Disk diffusion	34	amikacin, amoxicillin, ampicillin, cefazolin, cefotaxime, cefotaxime/clavulanic acid, cefoxitin, ceftazidime, ceftazidime/clavulanic acid, ceftriaxone, cefuroxime, cephalothin, chloramphenicol, ciprofloxacin, clarithromycin, clindamycin, doxycycline, erythromycin, gentamicin, imipenem, meropenem, nalidixic acid, nitrofurantoin, norfloxacin, novobiocin, ofloxacin, oxacillin, penicillin G, piperacillin, polymyxin B, tetracycline, tobramycin, trimethoprim/sulfamethoxazole, vancomycin
CLSI	MIC	3	cefotaxime, penicillin G, vancomycin
CLSI	ETEST	3	cefotaxime, penicillin G, vancomycin

8.2 Antibiotic Tests without Validated Breakpoints

The following antibiotics from JDWNRH dataset have no breakpoints for any organism.

Table 14. Antibiotics tested at the laboratory that have no breakpoints for any organism in the dataset.

amoxicillin_CLSI_Disk_25
cefotaxime/clavulanic acid_CLSI_Disk_30/10µg
ceftazidime/clavulanic acid_CLSI_Disk_30/4µg
cephalothin_CLSI_Disk_30µg
novobiocin_CLSI_Disk_5µg

JDWNRH reports few antibiotics tested that do not have breakpoints for *Staphylococcus aureus* and *Escherichia coli*. Testing these combinations is not a standard practice and thus not recommended by existing testing guidelines. The facility should stop testing these and frequently run WHONET reports to get updated results and recommendations.

Table 15. Invalid tests performed for *Staphylococcus aureus.*

Test method	Antibiotic	Number tested
Disk diffusion	oxacillin	1
Disk diffusion	vancomycin	10

Table 16. Invalid tests performed for *Escherichia coli.*

Test method	Antibiotic	Number tested
Disk diffusion	vancomycin	1

The most common reasons for invalid antibiotic tests include:

- The laboratory is testing incorrect antimicrobials (e.g., cephalexin), and they should be encouraged to switch to a similar antimicrobial with validated breakpoints (e.g., cephalothin).
- There is a mistake in the WHONET laboratory configuration, for example, choosing the wrong antimicrobial agent or choosing an incorrect disk potency.

In both circumstances, corrective action is indicated. If there is a mistake in the WHONET or BacLink configuration, this should be corrected. If the laboratory is performing incorrect testing, then education and review of purchasing and test practices would be indicated.

There are a few circumstances in which antimicrobials without validated clinical breakpoints would not be considered a testing mistake:

- The laboratory may be aware of published acceptable vendor-specific breakpoints that have not been evaluated by CLSI or EUCAST. In these cases, the user should manually enter the vendor-specific breakpoints into WHONET.
- The antimicrobial is tested for reasons that do not require clinical breakpoints; e.g., novobiocin or optochin are used for species identification, while ceftriaxone/clavulanic acid is used for ESBL confirmation.
- The laboratory may test an appropriate antibiotic, such as cefoxitin with *Staphylococcus aureus*, to predict the findings of another antibiotic that may be used in clinical therapy, such as methicillin or nafcillin. This has been described as proxy testing or surrogate testing.
- The laboratory is working collaboratively with CLSI or EUCAST to develop new breakpoints.
- The laboratory may not have sufficient resources to perform MIC testing when it is recommended, so the disk diffusion method is used instead to screen for resistance, for example *Staphylococcus aureus* and the vancomycin disk test. However, such results should not be considered reliable.

8.3 Antimicrobial Susceptibility Test Measurements

Measuring, recording, and analysing antimicrobial susceptibility test measurements, such as the disk diffusion, zone diameter and the MIC value are very important for the following reasons:

- To provide the correct test interpretation to the clinician.
- To compare old results with new results if the breakpoints change.
- To provide more detailed characterization of resistance mechanisms associated with high, moderate, and low levels of resistance.
- To conduct improved strain tracking.
- To assess the quality of laboratory test reagents and the quality of laboratory test performance.

The JDWNRH laboratory does not record the zone diameter, though it is recommended that facilities measure and record the zone diameter.

9 Quality Control Alerts

WHONET offers four different quality control alerts to facilitate the recognition of possible deficiencies in test performance. It is important to note that a quality control alert does not necessarily indicate that a result is incorrect. Therefore, repeat testing and confirmation are recommended before reporting these findings.

WHONET addresses four types of quality control alert:

- **Intrinsic resistance:** The organism is lacking a resistance characteristic typical of the species, for example *Klebsiella pneumoniae* susceptible to ampicillin.
- **Discordant test results:** In some cases, the results are biologically implausible, such as an *Escherichia coli* susceptible to ampicillin but resistant to ampicillin/sulbactam. In other cases, the results may be correct, but are relatively rare. For example, most isolates of *Escherichia coli* resistant to amikacin will also be resistant to gentamicin. However, in South America, there are many isolates have been confirmed to be amikacin resistant but gentamicin susceptible.
- **Rare resistance:** Resistance to some antimicrobials is extremely rare for some species and may suggest an error in the organism identification or in the antimicrobial susceptibility test result, such as *Staphylococcus aureus* resistant to vancomycin.
- **Incorrect test method:** There are some organisms and some organism-antibiotic combinations that should not be tested by certain test methods. For example, *Neisseria meningitidis* should always be tested by the MIC method. *Staphylococcus aureus* should not be tested with the oxacillin or vancomycin disk, and *Streptococcus pneumoniae* should not be tested by the oxacillin disk.

Table 17. Quality control alerts for unlikely and infrequent findings observed in the JDWNRH dataset shared with CAPTURA.

Organisms	Alert	Number of isolates	Priority	JD	JD2	BAC
Acinetobacter sp.	colistin or polymyxin = non-susceptible	5	Medium priority	3	2	
All organisms	penicillins = discordant results	1	Medium priority	1		
All organisms	quinolones and fluoroquinolones = discordant results	2	Medium priority	1	1	
Citrobacter sp.	cephalosporin III = susceptible	22	Low priority	14	7	1
Citrobacter sp.	penicillins or cephalosporin I or cephalosporin II or cephamycins = susceptible	23	Low priority	14	8	1
Enterobacter sp.	colistin or polymyxin = non-susceptible	2	Medium priority	2		
Enterobacter sp.	cephalosporin III = susceptible	42	Low priority	28	7	7
Enterobacter sp.	penicillins or cephalosporin I or cephalosporin II or cephamycins = susceptible	15	Low priority	10	4	1
Enterobacteriaceae	aminoglycosides = discordant results	30	Medium priority	13	6	11
Enterobacteriaceae	cephems = discordant results	30	Medium priority	17	9	4
Escherichia coli	colistin or polymyxin = non-susceptible	2	Medium priority	1		1
Klebsiella sp.	colistin or polymyxin = non-susceptible	2	Medium priority	1	1	
Klebsiella sp.	penicillins = susceptible	14	Low priority	9	3	2
Moraxella (B.) *catarrhalis*	ciprofloxacin = susceptible	2	Low priority		2	
Morganella sp.	penicillins or cephalosporin I or cephalosporin II = susceptible	36	Low priority	20	10	6
Neisseria meningitidis	antibiotic = tested by disk diffusion	1	Low priority	1		
Proteus sp.	colistin or polymyxin = susceptible	4	Medium priority	1	3	
Proteus sp.	tetracycline = susceptible	2	Low priority	1		1
Proteus vulgaris	penicillins or cephalosporin I or cephalosporin II = susceptible	10	Low priority	4	4	2
Pseudomonas aeruginosa	penicillins or cephems = susceptible	209	Low priority	113	66	30
Serratia sp.	cephalosporin III = susceptible	12	Low priority	5	6	1
Serratia sp.	penicillins or cephalosporin I or cephalosporin II or cephamycins = susceptible	1	Low priority	1		
Streptococcus pneumoniae	beta-lactams = tested by disk diffusion	169	Medium priority	85	54	30
Streptococcus viridans	penicillin or ampicillin = tested by disk diffusion	136	Low priority	61	60	15

Key Highlights from AMR Quality Report

- A limited number of CAPTURA essential variables are completely collected at JDWNRH.
- No quality control results were found in the JDWNRH dataset shared with CAPTURA. It is recommended that the hospital verifies the internal quality control program in place and ensures a record of such IQC activity to validate the results.
- Isolation of many fastidious organisms at the facility over the three reported years was observed. This observation identifies adequate laboratory capacity to identify important pathogens of public health importance that are usually difficult to grow in regular settings. However, the clinical correlation of the unusual organisms isolated in the laboratory should be made to avoid unnecessary use of antibiotics and prolonged treatments.
- JDWNRH tests a few antibiotics that do not have CLSI/EUCAST breakpoints for *Staphylococcus aureus* and *Escherichia coli*. Testing these combinations is not a standard practice and thus not recommended by existing testing guidelines.
- Antibiotics are not being tested consistently in JDWNRH. The frequency of antibiotic testing for *Staphylococcus aureus, Escherichia coli,* and other key organisms displays huge gaps. This makes it difficult to analyse AST patterns and trends over time.
- Many unlikely and infrequent resistance results have been identified in the dataset. These are highlighted as quality control alerts and require retesting/confirmation.

Metadata: Laboratory Questionnaire and RLQA

10 Laboratory Questionnaire

The Laboratory Questionnaire (also known as the AMR Questionnaire) captured basic information about the facility — including their capacity, availability of data and data capture/storage practices. The questionnaires helped the in-country team and the CAPTURA consortium to identify relevant facilities for further engagement.

The Laboratory Questionnaire completed in April 2020 indicated that the laboratory does cultures for blood, cerebrospinal fluid (CSF), soft tissue and body fluids, stool, and urine. The disk diffusion method is most often used for antimicrobial susceptibility testing (AST), and, on average, approximately 101-1,000 ASTs have been reported to be performed monthly. The laboratory holds 5 years of AST results in the record, in both paper and electronic formats. Collected variables are reported as the following (Table 18).

Table 18. List of variables collected as answered in the laboratory questionnaire. Please note that actual data collected at JDWNRH may contain different information.

CAPTURA Priority variables	**Variables Collected**
Sample Origin	Collected
Date of Birth/Age	Collected
Sex	Collected
Patient Location (Ward/Clinic)	Collected
Healthcare Facility Admission Date (if in-patient)	Collected
Healthcare Facility Admission Date of Visit (if out-patient)	Collected
Specimen Date	Collected
Specimen Type	Collected
Culture Result	Collected
AST Interpretation	Collected
AST Measurement	Collected
Specialized/Targeted variables (Optional CAPTURA Variables)	
Antibiotics Prescribed After Specimen Collection	Collected
Diagnosis (after laboratory results provided)	Collected
Patient Outcome	Collected
Date and Cause of Death (if applicable)	Collected
Additional/Recurrent Isolates/Infections	Collected
Additional Patient Information (e.g., change in initial therapy, date of discharge, comorbidities, date of discharge)	Collected

11 Rapid Laboratory Quality Assessment

Rapid Laboratory Quality Assessment (RLQA) was used to assess the capacity and quality of laboratories generating AMR data. RLQA is NOT a validated tool for assessing laboratory, but a tool developed by the project for project purposes: to gauge the quality of data and laboratory and assist in facility prioritisation for data collection.

RLQA consists of eight sections that sums up to 126 questions. The first seven sections include human resources, equipment availability, status of supplies, and quality control standards implemented while the last section requires a visual inspection to verify some of the responses provided. The responses of RLQA are now electronically stored, and each complete RLQA was scored via an automated scoring scheme. Summaries of scores and observations made in the RLQA are found in Table 19 and Figure 6.

Table 19. Summary of scores in RLQA with description of each section.

The microbiology laboratory at JDWNRH participated in the RLQA on May 9, 2020. The total score was 83.3, while the country median taken from 4 facilities across the country was 66.9. Facility section scores are shown below, with country median scores indicated in brackets for reference. *Country median scores haves been calculated from laboratories that participated in CAPTURA RLQA; they do not accurately represent the national medians.*		
Equipment	The Equipment section assesses the laboratory's access to the necessary equipment for conducting identification, antimicrobial susceptibility testing (AST), and performing internal quality control (IQC) over the past 3 years.	87.5 (72.9)
Staffing	The Staffing section evaluates the number of staff working in the laboratory, the level of qualification of senior staff, and the training that bench staff receives.	100.0 (57.5)
Media	Media section examines the type, source, and quality of the media used specifically for AST.	88.9 (76.8)
Identification	The Identification section examines how pathogens are tested, identified, and reported.	100.0 (72.5)
AST	The AST section assesses the laboratory's AST practices to understand which AST guidelines are followed, how closely current breakpoint guidance is adhered to, and how the laboratory captures AST data.	80.0 (73.5)
IQC	The IQC section assesses the laboratory's internal procedures for ensuring test validity and the reliability of equipment.	74.3 (76.2)
EQA	The EQAS section examines the laboratory's involvement in various EQAS and resulting scores.	33.3 (33.3)

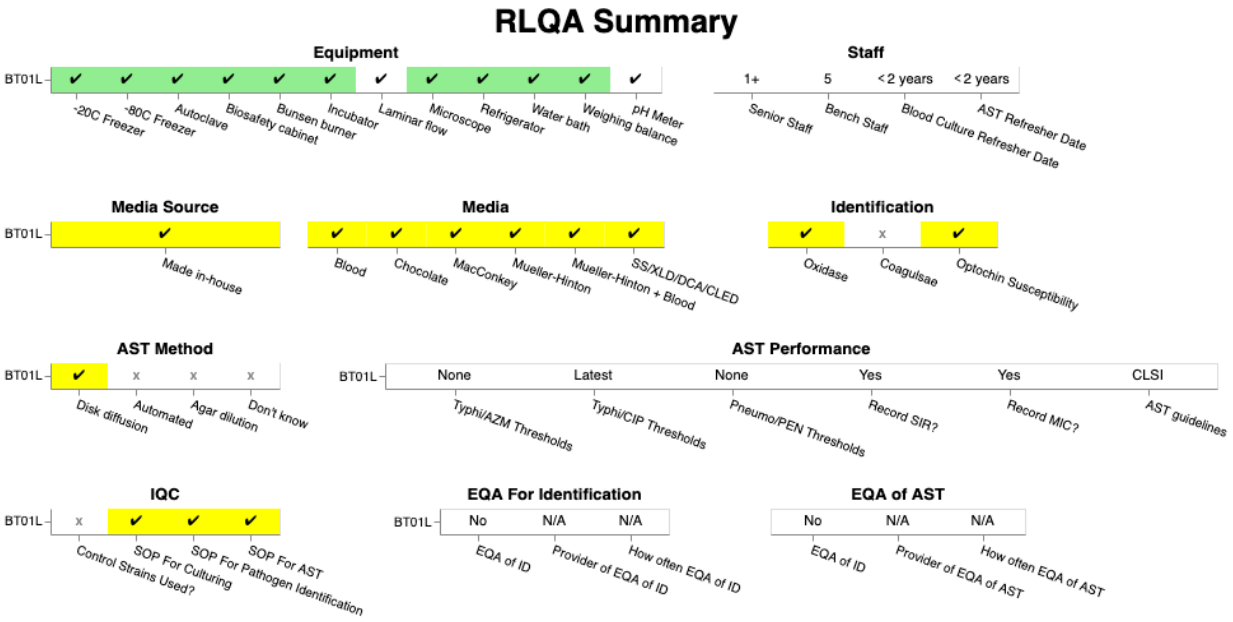

Figure 6. Summary of observations from RLQA conducted on May 9, 2020.

Key takeaway

As RLQA is not a validated tool, we suggest that the scores and observations presented above to be used as a cursory reference, and not for determining current quality and capacity of the laboratory. Please note that both Questionnaire and RLQA may now include outdated or inaccurate information, as laboratory improvements and strengthening activities may have taken place in between now and then. Upon the collection of the information, the project was also not able to validate the responses due to the limited time and resources available. We suggest using a validated assessment tool to verify and validate the observations presented above, and regarding the RLQA scores as a "quick snapshot" of the capacity noted by the project at the start of engagement.

Importantly, going forward, we recommend the facility to treat this experience with CAPTURA as a starting point to initiate a periodic collection of AMR metadata, which can be defined as, a set of data providing information about AMR data. AMR metadata, such as lab assessments, can be useful in understanding the data and systems in which the data was generated and collated. A comprehensive collection of AMR metadata ultimately provides contextual information, which in turn helps to curate/clean data and interpret analyses accurately.

Part III: AMU Data Analysis

AMU data findings

The antimicrobial usage (AMU) data in this report was collected through a piloting exercise of a template jointly created by CAPTURA and the in-country team. The exercised was based on both the WHO protocol on surveillance of antimicrobial consumption (AMC)[1] as well as adaptations from the WHO protocol on Point prevalence Surveys[2]. Since the initial dataset generated from this pilot is limited, the analysis presented in this report are preliminary and primarily meant to serve as an initial evaluation of the collection tool before further development and broader implementation. All curation, analysis, and visualizations were performed using R statistical software. A summary of AMU data is given on pages 24-25.

Data sources:
Antimicrobial use data was extracted from paper based Medical Records of admitted in-patients at JDWNRH hospital in Thimphu for selected months of the years 2018 (June, July, October, December) and 2019 (May – December). The data was downloaded from the Epicollect5 software and personal patient information, such as patient ID and age over 70, were encrypted.

It is important to note that the antimicrobial use in JDWNRH is likely higher than in other hospitals as it is a central referral hospital catering to more serious cases or patients requiring more specialized treatment often necessitating prescribing more and broader spectrum antimicrobials than in other settings and therefore cannot be generalized to the entire country.

12 Data overview

12.1 Before Curation

It is important to study the data to gain insight on its structure and completeness and to perform some basic visualizations and descriptive statistics. This was achieved using the Data Explorer package in R Studio. As it was noted that the exemplar data collected for 2018 was very limited, it was decided to only perform analysis for data from 2019.

An overview of the raw numbers of variables and observations and key missing data profile can be found in Tables 20 and Table 21, respectively. Each Row represents one unique patient. Columns contained information on prescriptions such as: antibiotic name, strength, form, route of administration, frequency, therapy start and stop date, infection site, treatment indication as well as specimen collection and microbiology laboratory data for the subset of patients (n=561) where a microbiology sample was taken. A variable recording 'appropriateness of antimicrobial prescribing' according to available country guidelines in terms of choice, dose, frequency, and duration was also recorded.

Table 20. Raw data Profile.

	Raw Data (2019)
Rows/ Observations	3,901
Columns/Variables	109
Missing Columns	17

Table 21. Basic data statistics.

Variable	Basic Statistic	Missing/Other
Age (mean)	33	14
Gender	Female (60.7%)	Others (0.2%)
Indication	Prophylaxis (50.7%)	UNK (1.1%) Other/NA (0.8%)
Ward	N=13 wards 1st Gynae & Obs. (28.5%)	
Sample Taken	Yes (15.4%)	28 (0.7%)
Route of Admin	Parenteral (69%)	7

[1] World Health Organisation. WHO methodology for a global programme on surveillance of antimicrobial consumption v1.0.
[2] (WHO) World Health Organisation. WHO Methodology for Point Prevalence Survey on Antibiotic Use in Hospitals v1.1. Geneva, 2018.

Table 22. Curation Steps.

Variable	Action towards analysis
COUNTRY	N/A
MONTH_of_DATA	N/A
YEAR_of_DATA	N/A
DISTRICT	N/A
HOSPITAL	N/A
DEPARTMENT	N/A
WARD	Recoded “Dental” and “Opthal” into “Others”
PATIENT_ID	N/A
AGE_in_YEAR	Merged into one variable named AGE (expressed in years) Recoded into AGE_GROUPS from Under 1 to Over 70 in 5-year increments Removed patients with no age information
AGE_in_MONTH	
AGE_in_DAY	
GENDER	Removed “Others” (n=8)
WEIGHT	N/A
DRUG_GENERIC_NAME 1-5	Transformed into long form and renamed as “name”. Removed missing values.
ATC 1-5	Removed missing values.
FORM 1-5	Removed missing values.
ROUTE_ADMIN 1-5	Recoded “Oral” = “O” | “IV” & “IM” = “P”. Assigned route of administration to the respective formulation when value missing. Removed "Inhalation" and "Nasogastric" and any missing values without respective formulation.
STRENGTH 1-5	Turned all into grams
STRENGTH_UNIT 1-5	Turned all into grams
DOSE 1-5	N/A
DOSE_UNIT 1-5	N/A
FREQ 1-5	N/A
FREQ_UNIT 1-5	N/A
START_DATE 1-5	Recoded as Character (There were formatting issues and was not used for analysis)
STOP_DATE 1-5	Recoded as Character (There were formatting issues and was not used for analysis)
INDICATION	Recoded "Unknown” to "other/NA" & spell checked
INFECTION_SITE	Missing variable recoded as Unknown
DIAGNOSES	N/A. Entered as free text
SAMPLE_TAKEN	Removed UNK & Missing
SAMPLE_TYPE 1-3	N/A
CUTURE_RESULT 1-3	N/A
ORGANISM 1-3	N/A
AST_PERFORMED	N/A
ASTR 1-10	N/A
ANTIBIOTIC_PANEL 1-10	N/A
TREATMENT_REVIEWED	N/A
APPROPRIATENESS	N/A

12.2 Curation

Table 22 gives an overview of the curation work for each variable. After initial curation, 3,651 patients were retained (individual observations were retained). As expected, some patients had more than one antibiotic prescribed, thus the total number of records of prescriptions was 7,386; of these, 58.2% (n=4,302) were prescribed to women. The majority (n=2,349) of antimicrobial prescriptions were given to women aged between 20-39 years old; this is a common pattern and is indicative that women of childbearing age are the most frequent recipients of antibiotics, usually in association with urinary tract infections and/or pregnancies and childbirth. The most prescribed antibiotic group (n= 3,438, 46.5%) was other beta lactams (carbapenems and cephalosporins), followed by beta-lactams and penicillins (1,894, 25.6%).

Over half of the patients (52.2%) were given an antibiotic treatment as a prophylaxis most often in surgical specialties such as Obstetrics/Gynecological (n=870, 82.5%), General Surgery (n=427, 51.5%), Orthopedic surgery (n=299, 72.9%). This reflects the standard practices of giving prophylaxis prior to delivery and/or surgeries, respectively.

In terms of antimicrobial prescriptions per ward, the majority of wards gave out prescriptions for primary infections with the exception of Obstetrics/Gynecological and Orthopedics. The surgical unit had a high level of antimicrobial prescriptions for management of primary infections (n=1134, 57.1% of their total prescriptions), followed by the medical ward (n=898, 84.2% of their total prescriptions) and the NICU (n=262, 89.1% of total prescriptions of the ward). The highest number of prescriptions given for indication of a hospital acquired infection were seen in the AICU and medical ward (n=38, 23.5%, and n=75, 7% of their total, respectively).

Overall, antimicrobial prescription was highest in the Surgical ward (26.9%) and closely followed by the Obstetrics/Gynecological ward (23.4%), then by Medical (14.4%), and Orthopedic surgery (8.9%). Antibiotics in the 'other beta-lactam' subgroups comprised the majority of antibiotics prescribed in most wards, with particularly high numbers prescribed in the Surgical, Orthopedic and Obstetrics/Gynecological wards. Among patients that had samples taken (n=561) most frequently samples were taken from patients admitted to the medical ward (32.4%).

When looking at proportion of samples taken by infection site (among patients prescribed antibiotic), lower respiratory, urinary (non-STI) and systemic infections were the most common infections where patients had biological samples collected (28.7%, 15.2% and 13.5%, respectively). In more than half of the cases where antimicrobials were prescribed a biological sample was never obtained for testing.

Table 23. Top Ten Antibiotics by route of administration and WHO AWARE Categorization.

No.	Oral	Parenteral
1.	Amoxicillin	Cefazolin
2.	Cephalexin	Ampicillin
3.	Doxycycline	Ceftriaxone
4.	Metronidazole	Metronidazole
5.	Azithromycin	Gentamicin
6.	Ciprofloxacin	Ciprofloxacin
7.	Cloxacillin	Cloxacillin
8.	Trimethoprim/sulfamethoxazole	Meropenem
9.	Nitrofurantoin	Piperacillin/tazobactam
10.	Erythromycin	Amikacin

When looking at the relative distribution of antimicrobial prescriptions according to AWaRe categories as indicated by WHO, there was some variation but across most departments the proportion of Access antimicrobials prescribed was well above 60 %. The Medical and Adult ICU awards were the only wards that did not meet the global target of 60% of antibiotic prescriptions to come from the Access category, however this is not unexpected in such wards in a tertiary facility. The AICU was also the department with the highest prescription of reserve antibiotics (3.1%). Of note, this finding conflicts with the national AMC data, where no consumption of Reserve antimicrobials was recorded. An AMC analysis was not conducted in the absence of appropriate denominator data and will be explored later in collaboration with the country team.

Evaluation of the appropriateness of prescriptions deemed that more than 80% of antimicrobial prescriptions in the NICU, Orthopedic, and Obstetrics/Gynecological departments were appropriate. Conversely, the number of prescriptions deemed least appropriate (below 60%) were seen in the Dermatology, AICU, and Medical units of the hospital. A relatively large proportion of cases where appropriateness was uncertain were also seen across these departments.

Although these findings require further investigation and validation, they could likely inform the focus areas of stewardship interventions in the facility.

As noted above, the AMU findings presented here are preliminary and mainly meant to be used for informing updates to the prospective data collection and analyses efforts planned within JDWNRH and other hospitals in Bhutan.

Appendix. Antibiograms

Gram-positive and Gram-negative Antibiograms

The antibiogram shows the cumulative antimicrobial susceptibility test statistics for Gram-positive and Gram-negative bacteria. The number of isolates tested is greater than or equal to 20. The official recommendation from the CLSI M39 document and others is at least 30 isolates, but 20 is still useful, especially in a low-resource setting with smaller data volumes, and for organisms of clinical importance.

Policymakers must be aware of problems in laboratory test quality and different types of bias due to patient presentation, sampling practices, and laboratory test practices. Routine microbiology laboratory data typically underestimates the incidence of microbial disease but overestimates the proportion of resistance.

Table 24. Gram-positive antibiogram. The numbers indicate % Susceptible.

Organism	Number of patients	AMK	AMP	CZO	FOX	CAZ	CRO	CHL	CIP	DOX
Staphylococcus aureus	1,431				84				65	97
Streptococcus pyogenes	430									
Coagulase-negative *Staphylococcus*	389				30					61
Enterococcus sp.	316		72							
Staphylococcus saprophyticus	264				31					
Streptococcus pneumoniae	188	34		100		92	91	94	80	
Streptococcus milleri	87									
Streptococcus viridans, alpha-haemolytic	62						78			
Streptococcus, beta-haemolytic	26									

Table 25. Gram-positive antibiogram, continued. The numbers indicate % Susceptible.

Organism	Number of patients	ERY	GEN	NIT	NOR	OXA	PEN	TCY	SXT	VAN
Staphylococcus aureus	1,431	58					5	96	76	
Streptococcus pyogenes	430	69					100			
Coagulase-negative *Staphylococcus*	389	28					8	72	50	
Enterococcus sp.	316			95	41		59			98
Staphylococcus saprophyticus	264			97	97		16	90	86	
Streptococcus pneumoniae	188	92	60			96	99	57	53	
Streptococcus milleri	87	75					93	84		
Streptococcus viridans, alpha-haemolytic	62	44					77	66		
Streptococcus, beta-haemolytic	26	62					100			

Table 26. Gram-positive organisms tested against the following antimicrobials were included in the antibiogram.

Code	Antibiotic	Code	Antibiotic	Code	Antibiotic
AMK	amikacin	CHL	chloramphenicol	NOR	norfloxacin
AMP	ampicillin	CIP	ciprofloxacin	OXA	oxacillin
CZO	cefazolin	DOX	doxycycline	PEN	penicillin G
FOX	cefoxitin	ERY	erythromycin	TCY	tetracycline
CAZ	ceftazidime	GEN	gentamicin	SXT	trimethoprim/sulfamethoxazole
CRO	ceftriaxone	NIT	nitrofurantoin	VAN	vancomycin

Table 27. Gram-negative organisms tested against the following antimicrobials were included in the antibiogram.

Organism	Number of patients	AMK	AMP	CZO	CAZ	CRO	CHL	CIP	DOX	ERY	GEN	IPM
Escherichia coli	6,513		29	24		60					93	
Klebsiella pneumoniae	1,336			23		45		42			80	
Acinetobacter sp.	504	66			13	19		25	68		36	31
Pseudomonas aeruginosa	482				65			66			81	
Haemophilus influenzae	200		84			95	60	96				
Klebsiella oxytoca	133	64	4	14		35		40			78	43
Pseudomonas sp.	133	62			49			55			74	39
Enterobacter sp.	93	71	13	5		41		53			76	43
Salmonella sp.	78		91			96	100	83				
Proteus mirabilis	62		57	34		77		48			84	
Proteus vulgaris	56		13	11		76		84			86	
Moraxella sp.	45		83					86		73		
Klebsiella aerogenes	44			13		46		74			73	
Citrobacter sp.	31		7	4		37		45			84	
Enterobacter cloacae	27		4			43		48			73	

Table 28. Gram-negative organisms tested against the following antimicrobials were included in the antibiogram, continued.

Organism	Number of patients	IPM	MEM	NAL	NIT	NOR	PIP	POL	TCY	TOB	SXT
Escherichia coli	6,513				93	60					51
Klebsiella pneumoniae	1,336				48	69					50
Acinetobacter sp.	504	31	70				4	95		46	34
Pseudomonas aeruginosa	482						44				
Haemophilus influenzae	200										65
Klebsiella oxytoca	133	43			52	56		100			47
Pseudomonas sp.	133	39	48				48				
Enterobacter sp.	93	43			56	73					58
Salmonella sp.	78			69					81		97
Proteus mirabilis	62					90					68
Proteus vulgaris	56					75					72
Moraxella sp.	45								96		50
Klebsiella aerogenes	44										70
Citrobacter sp.	31										62
Enterobacter cloacae	27										62

Table 29. Gram-negative antibiogram. % Susceptible, first isolate per patient.

Code	Antibiotic	Code	Antibiotic	Code	Antibiotic
AMK	amikacin	DOX	doxycycline	NOR	norfloxacin
AMP	ampicillin	ERY	erythromycin	PIP	piperacillin
CZO	cefazolin	GEN	gentamicin	POL	polymyxin B
CAZ	ceftazidime	IPM	imipenem	TCY	tetracycline
CRO	ceftriaxone	MEM	meropenem	TOB	tobramycin
CHL	chloramphenicol	NAL	nalidixic acid	SXT	trimethoprim/sulfamethoxazole
CIP	ciprofloxacin	NIT	nitrofurantoin		

-End of report-